REMARKS/ARGUMENTS

In response to the Office Action of December 20, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39 and 44-46 have been amended. Claims 2-38 were cancelled in a previous response (filed on July 28, 2005). Claims 39-43, 45 and 46 are withdrawn from consideration. Claim 44 is withdrawn from consideration in part to the extent of the antibody. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time.

Claims 1 and 44 are currently under examination. Claim 44 is under examination only in part to the extent of the peptide consisting of SEQ ID NO:1. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

The title of the invention has been amended to correct a typographical error (CENE-E to CENP-E) and to clarify that the biopolymer marker is indicative of Alzheimer's disease; see the

instant specification at page 46, lines 2-5.

The "Background of the Invention" section has been amended to correct a punctuation error at page 1, line 23.

The description of the reference at page 5 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The paragraph at page 24 has been amended to correct a typographical error (luymph to lymph).

The description of Figure 1 at page 37 has been amended to correct a punctuation error (Alzheimers to Alzheimer's).

The description of Figure 2 at page 37 has been amended to add the sequence identification number, SEQ ID NO:1, to the disclosed marker and to clarify that the figure shows the characteristic mass spectral profile of SEQ ID NO:1.

The protocols at pages 40-44 have been amended to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF). The protocol titles at page 41 (lines 5 and 19), page 42 (line 11) and page 43 (lines 1 and 14) were underlined in the original disclosure and with the exception of the term "SEPHAROSE" at page 41, line 19 and page 42, line 11, do not indicate text amended herein.

The paragraph at page 46 has been amended to correct a

punctuation error (Alzheimers to Alzheimer's) and to add the sequence identification number, SEQ ID NO:1, to the sequence disclosed.

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 49, line 3 in order to provide explicit support for cerebrospinal fluid as recited in claim 41. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. A typographical error within the same paragraph has also been amended (skill replaced skilled).

The abstract has been amended to remove the legal phraseology ("said").

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to indicate that the claimed biopolymer marker evidences a link to Alzheimer's disease; see the instant specification at page 35, lines 14-18, page 46, lines 2-5 and Figures 1 and 2.

Claim 39 has been amended to clearly disclose the relationship between the presence of the claimed biopolymer marker (SEQ ID NO:1) and Alzheimer's disease. Claim 39 has also been amended to explicitly indicate how the presence of the claimed biopolymer marker is determined from mass spectral profiles. The changes to

claim 39 find basis throughout the specification as originally filed, see, for example, page 35, lines 14-18, page 46, lines 2-5 and Figures 1 and 2. Claim 39 has also been amended to clarify that mass spectrometry is conducted to identify peptides contained in samples which have been obtained from patients; see the instant specification at page 46, lines 13-15.

Claim 44 has been amended to correspond with the biopolymer marker of claim 1 (as amended herein). Support for various types of kits can be found in the original disclosure, see for example, page 36, lines 9-12 and page 47, line 1 to page 48, line 19. Claim 44 has also been amended to clarify that the sample is obtained from a patient; see the instant specification at page 46, lines 13-15.

Claims 45 and 46 have been amended to provide proper antecedent basis for the term "kit" in claim 44 (as amended herein).

Restriction

Applicants elected Group I, with traverse, for prosecution on the merits in the response filed on July 28, 2005. Group I includes claim 1 and claim 44. Claim 44 is included only in part to the extent of the peptide consisting of SEQ ID NO:1.

In the Office Action mailed on November 4, 2003, the Examiner

asserts that the claims encompass inventive groups directed to different products. The Examiner separates the elements of the claimed kit, peptide and antibody, into two groups. A claim should not be evaluated by an analysis of each individual part, but should be evaluated as a whole. Applicants respectfully point out to the Examiner that claims 44-46 are drawn to a kit as a product, i.e. the kit is the single product. Thus, in this instance, SEQ ID NO:1 and the antibody that binds to it do not represent different products. Therefore, Applicants submit that the separation of claims 44-46 into a peptide group and an antibody group is improper, and respectfully traverse the requirement for restriction.

Furthermore, considering that claims 39-46 are limited to the use of the biopolymer marker of claim 1 (SEQ ID NO:1); a search of these claims would encompass this marker. Thus, Applicants respectfully submit that the search requirement is, in fact, co-extensive, and further traverse the requirement for restriction.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NO:1 a search of these claims would encompass this specific peptide. The instant application is related in claim format to several other applications, both pending and issued, of which

serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker peptide of SEQ ID NO:1 is found to be novel, methods and kits limited to its use should also be found novel.

Objection to the Specification

The disclosure stands objected to because of the following alleged informalities:

The Examiner acknowledges proper submissions of CRF and paper copies of the Sequence Listing; however, asserts that the specification lacks appropriate conformance with the Sequence Rules which require referral to appropriate SEQ ID NO'S when referencing amino acid sequences, see in particular page 46. The Examiner requires appropriate correction.

The instant specification, at both the Brief Description of the Figures section and at page 46, has been amended to include the sequence identification number (SEQ ID NO:1) for the amino acid

sequence disclosed therein.

Applicants respectfully submit that the instant application is now in conformance with the Sequence Rules and respectfully request that the objection to the disclosure be withdrawn.

Objection to the Claims

Claims 1 and 44 (in part), as presented on July 28, 2005, stand objected to because of the following alleged informalities:

The Examiner asserts that the claims assert that SEQ ID NO:1 is diagnostic for Alzheimer's disease and that the peptide provides an Alzheimer's disease diagnostic kit. The Examiner asserts that these recitations are objected to because these uses are not evidenced. The Examiner requires appropriate correction.

Applicants respectfully disagree with the Examiner's determination and address this issue below in the sections regarding the rejection of the claims.

Rejection under 35 USC 101

Claims 1 and 44 (in part), as presented on July 28, 2005, stand rejected under 35 USC 101 because the claimed invention is allegedly not supported by either a specific and substantial asserted utility or a well established utility.

Applicants respectfully disagree with the Examiner's

contention and assert that the claimed invention has a specific and substantial asserted utility and a well established utility.

The claimed biopolymer marker (SEQ ID NO:1) is useful for diagnosis and treatment of Alzheimer's disease since it was found to evidence a link to Alzheimer's disease (an "asserted" utility). This asserted utility is supported by data, the gel shown in Figure 1, derived from the working examples which shows that the claimed peptide (SEQ ID NO:1) is differentially expressed between Alzheimer's disease patients and patients age matched with the Alzheimer's disease patients.

The Examiner acknowledges that the peptide consisting of SEQ ID NO:1 is asserted as being diagnostic for Alzheimer's disease. The Examiner further acknowledges that diagnosis of Alzheimer's disease is a specific utility. However, this utility is not specific **and substantial** as a use in diagnosis is not reasonably confirmed(emphasis added by Examiner).

Applicants respectfully disagree and remind the Examiner that an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement under 35 USC 101 (see MPEP 2107.02 III A). Thus, the requirements of 35 USC 101 are met solely by Applicants' assertion regarding the use of the claimed peptide (SEQ ID NO:1) as a diagnostic marker for Alzheimer's disease.

Applicants' statement of an asserted utility also constitutes a specific and substantial utility that is supported by the specification as originally filed; see page 1, lines 5-13, page 35, lines 14-18, page 46, lines 2-5 and Figures 1 and 2).

The claimed biopolymer marker (SEQ ID NO:1) does not evidence a link to a myriad of unspecific diseases but rather evidences a link to a specific disease, Alzheimer's disease, thus, the invention has a specific utility.

Although Applicants believe that the instant specification, as originally filed, fully supports the claim that an isolated biopolymer marker consisting of SEQ ID NO:1 is diagnostic for Alzheimer's disease, in the interest of compact, efficient prosecution, Applicants have removed the term "diagnostic" from the claims and note that the isolated biopolymer marker consisting of SEQ ID NO:1 is linked to Alzheimer's disease. Thus, claim 1 has been amended to recite that the isolated biopolymer marker, SEQ ID NO:1, evidences a link to Alzheimer's disease.

According to the web site dictionary.com the term "linked" refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 1). Applicants respectfully assert that the instant specification fully supports a connection and/or an association of the claimed biopolymer marker (SEQ ID NO:1) with Alzheimer's disease. The

claimed biopolymer marker (SEQ ID NO:1) was identified as related to Alzheimer's disease by carrying out the protocols disclosed in the specification (see page 46, lines 2-5 of the instant specification as originally filed). The data presented in Figure 1(as originally filed and as attached to the declaration filed herewith) clearly evidences that the claimed biopolymer marker (SEQ ID NO:1) was found to be differentially expressed between Alzheimer's disease patients and patients age matched with the Alzheimer's disease patients. Thus, Applicants assert that the claimed biopolymer marker (SEQ ID NO:1) is useful for diagnosis and treatment of Alzheimer's disease.

In the search for specific biomarkers, proteins found to be differentially expressed between "disease" and "normal" are frequently identified as potential targets for diagnostics and/or therapeutics. Accordingly, one of skill in the art would believe that differential expression is sufficient information to associate a peptide with a disease.

For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar Conference on Mass Spectrometry (see attached article, Physiological Genomics 2:59-65 2000; reference 2). This conference took place in 2000, thus coinciding with the time that the instant inventors were working to develop the instant invention.

In the disclosed method of the instant invention, proteins (as observed on a gel) that are identified as differentially expressed between a disease and a non-disease state are selected for excision (from the gel) and identification (see, for example, page 38, lines 6-10 of the instant specification as originally filed, and Figure 1). Such selection methods are common practice in the search for biomarkers of specific physiological states. For example, at page 61, right column of Patterson, several automation processes are discussed in the section titled "Automated identification of gel-separated proteins by mass spectrometry". This discussion begins with the following statement:

"Following quantitative analysis of 2-DE patterns, the next step is the identification of all protein spots that display differential expression."

Thus, it is concluded that it is known practice to select potential disease markers by their differential expression between a disease and a non-disease state.

Furthermore, Applicants respectfully submit that many of the methods disclosed in the instant specification are routinely practiced by those of ordinary skill in the art attempting to identify biomarkers of particular physiological states. For example, at page 64, left column of Patterson is a description of the SELDI approach (as discussed at the conference by Scot

Weinberger) wherein defined chemical/biochemical surfaces are utilized to allow fractionation of proteins from biological fluids in a reproducible manner. This reproducibility allows comparisons between different samples to be made. Weinberger described a search for markers of benign prostate hyperplasia that, like prostate cancer, displays elevated prostate specific antigen (PSA) levels. The fraction exhibiting a difference between these samples was able to be enzymatically digested, and a number of peptides were generated. These peptides were able to be fragmented using the MALDI-Qq-TOF(a procedure described by Ken Standing at the conference, page 62, left column of Patterson). It was found that there appears to be a difference in the relative level of seminogelin fragments between these two states (prostate cancer and benign prostatic hyperplasia), thus providing a potential differential marker.

Applicants respectfully draw the Examiner's attention to the fact that the method described by Weinberger is analogous to the method described in the instant specification. Furthermore, when interpreting data Weinberger uses the same approach to interpretation as the instant inventors in order to identify seminogelin fragments as a potential marker to distinguish between benign prostate hyperplasia and prostate cancer based on differential expression of the fragments. Additionally, Applicants

respectfully point out to the Examiner that Weinberger linked differential expression of seminogelin to benign prostate hyperplasia and prostate cancer without analysis of a sample from a control patient free of disease or analysis of a sample from a patient having another disease, which is not benign prostate hyperplasia or prostate cancer. Such linking of markers with disease through differential expression is commonly practiced in proteomics.

By asserting that the use of the claimed biopolymer in diagnostics of Alzheimer's disease is not reasonably confirmed, it appears that the Examiner is requiring Applicants to show evidence that the claimed biopolymer marker (SEQ ID NO:1) is definitively diagnostic for Alzheimer's disease.

Applicants respectfully submit that the Examiner is requiring Applicants to meet a standard higher than that which is necessary to show that an invention has utility.

Applicants remind the Examiner that the utility threshold is not high and that the stringency of evaluating evidence related to utility is well established. For example, an applicant is not required to provide evidence sufficient to establish that an asserted utility is "true beyond a reasonable doubt". Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted

utility is more likely than not true; MPEP 2107.02 VII. The "confirmed" evidence and/or further experimentation apparently required by the Examiner would provide much more information than what is needed in order to ascertain whether something is more likely than not true. The evidence must simply be convincing for one to conclude that something, in the instant case, the usefulness of the claimed peptide (SEQ ID NO:1) as a marker for Alzheimer's disease, is more likely than not true.

As discussed above, one of ordinary skill in the art would recognize differentially expressed peptides to be potential markers for a disease condition. Another example, US 6,124,108, issued to Prabhati Ray on September 26, 2000, discloses a protein biomarker for mustard chemical injury (see attached copy of patent; reference 3). Upon electrophoretic separation of an extract of human skin cells, Ray immediately identified a protein band found at 50,000 to 80,000 daltons as a biomarker (see abstract and column 2, lines 1-25). Analogous to the disclosed uses of the biopolymer marker of the instant invention, Ray also indicated that his biomarker can be used to raise antibodies or may be used in a kit for identifying the presence or absence of the marker (see abstract).

The differential expression of the peptide is the convincing property which leads one of skill in the art to recognize the peptide as a marker. Since the utility standard only requires

evidence to be convincing rather than fully conclusive and further, those of skill in the art are convinced that differential expression identifies biomarkers, then the differential expression of the claimed peptide (SEQ ID NO:1) should be deemed sufficient evidence to convince one of skill in the art that the claimed peptide is more likely than not a marker for Alzheimer's disease.

The Examiner asserts that presumably the figure shows that the peptide consisting of SEQ ID NO:1 was present in Alzheimer's disease samples in comparison to controls.

Applicants respectfully submit that the Examiner's presumption is incorrect. SEQ ID NO:1 was found to be differentially expressed, however, it was found to be present in age matched control samples and absent in Alzheimer's disease samples.

In order to satisfy the requirements of 35 USC 101, an invention must be "useful". A "useful" invention is an invention that one of skill in the art can use in a manner which provides some immediate benefit to the public (see MPEP 2107.01 I and *Nelson v. Bowler* 206 USPQ 881).

The instant specification discloses how the claimed biopolymer marker (SEQ ID NO:1) was identified and provides the mass spectral profile of this biopolymer marker (shown in Figure 2) for use as a reference for comparison with mass spectral profiles obtained from unknown samples. Assays using this mass spectral profile can

be immediately applied for the benefit of the public and thus, in compliance with the utility standard, the instant invention is useful in its currently available form.

The claimed biopolymer marker (SEQ ID NO:1) was identified in the following manner:

Proteins contained within the sera samples are often too large (>3kd) to be effectively resolved by most forms of mass spectrometry, thus the samples can first be resolved by polyacrylamide gel electrophoresis. Samples to be compared, e.g. disease state versus normal, are usually run side by side in the gel. Once the proteins have been resolved and visualized with stains, the proteins (represented by bands)that differ between the two compared states (disease versus normal) can be excised from the gel for further purification and identification. The excised bands are then cleaved by enzymes into fragments smaller than 3kd and the fragments are further purified by some form of chromatography; C18 ZIPTIP, column flow-through, column elution stream, and/or column scrub stream. See the instant specification as originally filed at page 25, line 16 to page 26, line 22; page 37, line 10 to page 40, line 5; for specific chromatographic protocols, page 40, line 11 to page 46, line 1. The purified fragments (peptides) are then sequenced by mass spectrometry. These peptides, which are fragments of the original protein obtained from the sample, are sequenced to

form a spectral pattern composed of parts of the peptide. The spacing in terms of mass between the parts of the peptide is unique and is referred to as the "fragmentation pattern". See the instant specification as originally filed at page 38, line 19 to page 39, line 9.

The proteolytic cut sites within a protein can be predicted from the translated amino acid sequence. The mass of the peptides that result from the predicted cutting can be calculated and the theoretical fragmentation pattern determined. The mass spectral profile, i.e. peptide mass and fragmentation pattern, obtained from the experiments, is compared to a database containing theoretical fragmentation patterns and is identified by best match. See the instant specification as originally filed at page 39, line 11 to page 40, line 5. It is important to point out that mass spectral profiles are reproducible; many have been published and may be used as references for identification of unknowns.

The mass spectral profile of the claimed biopolymer marker (SEQ ID NO:1) provided in Figure 2 can be compared to mass spectral profiles obtained from unknown samples. The mass spectral profile of the claimed biopolymer marker has an ion peak at about 1594 daltons and the presence of the biopolymer marker is confirmed by the identification of this ion peak in a mass spectral profile obtained from a sample. Identification of this mass spectral

profile links the sample to Alzheimer's disease, for example, if the mass spectral profile shown in Figure 2 is found in a mass spectral profile obtained from an unknown sample, then the sample can be linked to Alzheimer's disease.

Thus, contrary to the Examiner's assertion, the instant invention is complete and thus, practice of the invention does not require "further undue experimentation". The instant specification already evidences that the claimed biopolymer marker can distinguish Alzheimer's disease from a normal physiological state and provides a tool, the mass spectral profile shown in Figure 2, which can be used by one of ordinary skill in the art as a reference for comparison with mass spectral profiles obtained from unknown samples. Since the instant specification provides the information and the tool required to use the claimed peptide as a marker for Alzheimer's disease, there is no need for one of skill in the art to experiment to determine if the peptide could be used to diagnose Alzheimer's disease.

Thus, this identified marker can be used as a marker for Alzheimer's disease, i.e. by testing unknown samples for the presence of the marker. Alternatively the disclosed methods can be used to identify markers in another disease condition. The information disclosed in the instant specification, such as that on page 5, lines 12-20 and page 11, lines 9-20, is disclosed to

indicate how the claimed biopolymer marker (SEQ ID NO:1) was evaluated and is meant to teach one of ordinary skill in the art how to use the disclosed methods as a template to duplicate the findings of the instant inventors or to identify other peptide markers.

The relationship between the claimed marker (SEQ ID NO:1) and Alzheimer's disease depends upon the differential expression of the claimed marker between patients having Alzheimer's disease and age matched control patients (for example, see page 1, lines 5-13, page 38, lines 6-10 and page 11, lines 9-20 of the instant specification as originally filed). One of ordinary skill in the art would be able to determine the nature of this relationship from simple observation of a gel such as that shown in Figure 1; for example, in the instant case, the claimed peptides are present in age matched samples and absent in Alzheimer's disease samples, however in another disease condition a marker may be in present in the disease and absent in the normal or present in both disease and normal at different levels.

The instant inventors isolated the claimed peptide (SEQ ID NO:1) by carrying out the disclosed protocols (chromatography and mass spectrometry) on samples obtained from Alzheimer's disease patients and healthy patients age matched with the Alzheimer's disease patients, noted the expression in age matched patients

relative to lack of expression in Alzheimer's disease patients, subjected the noted expression pattern to the criteria as disclosed at page 11, lines 9-20 of the instant specification, decided that the peptides show stronger expression in the age matched patients as compared to expression in the Alzheimer's disease patients, and, thus identified the peptide (SEQ ID NO:1) as a marker linked to, and possibly predictive of Alzheimer's disease. The mass spectral profile established for the claimed biopolymer marker is presented in Figure 2. Mass spectral profiles are reproducible, many have been published for reference purposes. Thus, as discussed above, the mass spectral profile of the claimed peptide as disclosed in Figure 2 is intended to be used as a reference for evaluation of unknown samples, and, as such is to be considered a diagnostic tool. Accordingly, contrary to the Examiner's assertions, a skilled practitioner would not be required to engage in significant further research to establish if the claimed peptide can be used as a marker for Alzheimer's disease since the instant specification discloses the mass spectral profile of the claimed peptide (Figure 2) and teaches its use as a diagnostic tool.

The Examiner makes several assertions regarding Figure 1. The molecular weight bands of the gel are not visible and moreover the labeling of the figure is inconsistent to show isolation of the 15 mer in disease samples in comparison to controls. The Examiner can

find no detailed characterization of the samples that were tested that correspond to Alzheimer's disease samples, or the methodology used to characterize and/or distinguish Alzheimer's samples from controls. The labeling of the figure is confusing as it identifies both Band 1B and Band 4 as CENP-E. The Examiner asserts that even more confusing is CENP-E is an art recognized protein of over 2600 amino acids in length, see in particular Nature 359:536-539 1992, corresponding to a molecular weight of over 90kDa.

Applicants respectfully submit that the Examiner's comments reveal an incomplete understanding of the invention.

Figure 1 is a photograph of a gel showing protein bands which have been prepared for mass spectrometry by DEAE chromatography (elution). The proteins were obtained from nine samples (lanes read from the left); lanes 1-4 contain samples obtained from Alzheimer's disease patients (ADH-004, ADH-005, ADH-006 and ADH-008); lanes 5-8 contain samples obtained from patients age matched with the Alzheimer's disease patients (ADC(H)-002, ADC(H)-003, ADC(H)-004 and ADC(H)-005); lane 9 contains a serum sample pooled from several normal, healthy patients (pooled NHS, i.e. normal human serum) and lane 10 contains the high molecular weight standard markers. Band 1B, from which fragments of the CENP-E protein were identified, is present in all of the age matched samples (lanes 5-8). Band 4, from which fragments of the CENP-E protein were identified, is present

in three of the age matched samples (lanes 5-7). Bands 1B and 4 are not found in any of the Alzheimer's disease samples or in the pooled NHS sample.

According to the method of the invention, the criteria for evaluation can be considered two-fold, involving both the direct appearance of bands in the gel and the identification of specific ions and/or peptides from the bands appearing in the gel. The bands are selected for further analysis and identification based on differential expression between physiological states as observed in gels; i.e. presence of band in one state versus absence in the other and/or increase in one state versus decrease in the other (see page 26, lines 6-13 of the instant specification). The peptides contained within the bands are ultimately identified by mass spectrometry, not by gel electrophoresis alone.

Contrary to the Examiner's assertions regarding Figure 1, the molecular weight markers are clearly visible in lane 10 of the gel and the relevant bands are pointed out by arrowheads. Each band is clearly labeled with the names of proteins whose fragments were identified therein. The samples tested which correspond to Alzheimer's disease samples are, as the figure title/lane labeling indicates, obtained from patients age matched with the Alzheimer's disease patients.

As evidenced by the discussion in the above paragraphs, the

methodology used to characterize/distinguish the samples is clearly described in the specification. In the methods of the instant invention, large proteins, such as CENP-E, are identified by identifying individual peptide fragments (see the specification at pages 37-40). Thus, it can be expected that fragments of the same protein will be identified from multiple bands, as in the instant case, wherein fragments of CENP-E were identified in Bands 1B and 4.

A hypothetical example may serve to clarify the described methods. For example, a researcher has found that Band G and Band K are differentially expressed between a lung cancer patient and a patient determined to be healthy with regard to lung cancer. In hope of identifying potential markers for lung cancer, the researcher subjects Bands G and K to mass spectrometry and obtains three distinct mass spectral profiles. Two of these mass spectral profiles reveal sequences which match to known proteins, Protein A and Protein W, that the researcher then identifies as potential markers for lung cancer. Peptide sequences matching to Protein A were isolated from Band K and peptide sequences matching to Protein W were isolated from both Bands G and K. The researcher can then compare the mass spectral profiles of Proteins A and W to mass spectral profiles obtained from patients suspected of having lung cancer in order to determine the presence of the markers, i.e.

Protein A and/or Protein W. The fact that multiple peptides can be identified from the same band or that the same peptide can be identified from multiple bands does not diminish the value of the peptides as markers since it is the mass spectral profiles which are unique and not the bands themselves. If a peptide is identified in a particular band, then it is present in the band regardless of the presence and/or the absence of other peptides/proteins within the same band. In the instant case, Bands 1B and 4 were found to be differentially expressed between Alzheimer's disease patients (lanes 1-4 of the gel shown in Figure 1) and patients age matched with the Alzheimer's disease patients (lanes 5-8 of the gel shown in Figure 1). Thus, Bands 1B and 4 were subjected to analysis using mass spectrometry and found to contain peptides that match to portions of the sequence of CENP-E protein (see labeling of Bands 1B and 4 in Figure 1). These peptides were identified as linked to Alzheimer's disease based upon their differential expression between Alzheimer's disease and age matched controls.

In order to further illustrate this point and to more clearly present the gel from which the claimed biopolymer marker (SEQ ID NO:1) was obtained, Applicants provide the attached declaration with figure entitled "DEAE 5(E) Ad vs. Age Matched AD" which represents Figure 1 as originally filed. The attached figure was produced by scanning the original photograph of the gel. The

figure is entitled "DEAE 5(E) Ad vs. Age Matched AD" and represents Figure 1 as originally filed. No new matter has been added; this figure is simply a clearer copy of Figure 1 as originally filed and is provided to clarify the presence and absence of the bands. Expression of Bands 1B and 4 is evident in samples obtained from patients age matched with the Alzheimer's disease patients (lanes 5-8, as read from the left) and is not evident in samples obtained from Alzheimer's disease patients (lanes 1-4) or in the sample of pooled NHS (lane 9). Thus, the gel provides evidence that the claimed peptide (SEQ ID NO:1) is differentially expressed between Alzheimer's disease and age matched controls. The gel shown in the figure does not represent new experimentation; the figure shows a clearer image of the original gel made at the time that the experiments described in the instant specification were first carried out.

The Examiner asserts that there is no data that evidences the short peptide amongst the others and concludes that the specification provides no evidence that the 15-mer is diagnostic to Alzheimer's disease.

Applicants respectfully disagree with the Examiner's determination and remind the Examiner that it has been established that where an applicant has specifically asserted that an invention has a particular utility, the assertion cannot be simply dismissed

by Office personnel as being "wrong", even when there may be a reason to believe that the assertion is not entirely accurate (see MPEP 2107.02 III B).

The figures provide evidence that the claimed biopolymer marker is linked to Alzheimer's disease as Figure 1 evidences that the claimed biopolymer marker (SEQ ID NO:1, a fragment of the CENP-E protein) was differentially expressed between Alzheimer's disease and age matched controls and Figure 2 shows the unique mass spectral profile which identifies SEQ ID NO:1 (the claimed biopolymer marker).

Thus, Applicants respectfully assert that it is improper for the Examiner to state that the 15-mer (the claimed biopolymer marker) is not diagnostic for Alzheimer's disease, especially since the specification provides data, Figures 1 and 2, which suggests that it most likely is diagnostic for Alzheimer's disease.

According to the instant invention, the criteria for labeling a peptide a "marker" is differential expression in disease vs. normal. The claimed biopolymer marker (SEQ ID NO:1) is differentially expressed in tissue samples from Alzheimer's disease patients and patients age matched with the Alzheimer's disease patients. Stedman's Medical Dictionary defines the term "marker" as a physiological substance, that when present in abnormal amounts in the serum may indicate the presence of disease (see attached

definition as accessed from the internet at dictionary.com; reference 4). Thus, it is acceptable in the art to identify a protein as a marker based simply on the presence of abnormal amounts, no extension validation is required. For example, Cheng et al. (see attached abstract, Journal of Neural Transmission 103 (4):433-446 1996; reference 5) identify homovanillic acid as a useful marker for early diagnosis of Parkinson's disease since when comparing the levels of homovanillic acid in cerebrospinal fluid, they found a lower level in Parkinson's disease patients as compared with the levels found in age-matched controls.

Thus, Applicants respectfully submit that, contrary to the Examiner's assertion, it is obvious why a worker of ordinary skill in the art would refer to the claimed peptide (SEQ ID NO:1) as a marker for Alzheimer's disease.

It has been established that evidence of the "usefulness" of an invention does not require absolutely definitive results, as the MPEP states at 2107.01 that in order to satisfy the requirements of 35 USC 101, an applicant must show that the claimed invention is "useful" for some purpose either explicitly or implicitly.

The showing of a link between a peptide and a disease implies the potential for use of the peptide for diagnosis and/or therapeutics of the disease. For example, Blennow et al. (Dementia 6(6):306-311 1995; reference 6) suggest, based on differential

expression, that chromogranin in cerebrospinal fluid has a potential as a biochemical marker for synaptic degeneration in AD type I.

Thus, even if the only information obtained from identifying the presence of marker SEQ ID NO:1 is the determination of a link to Alzheimer's disease, Applicants respectfully submit that such information would be enough to establish the utility of the instant invention since the showing of a link between the claimed peptide (SEQ ID NO:1) and Alzheimer's disease implies the potential for use of the claimed peptide for diagnosis and/or therapeutics of Alzheimer's disease.

Claim 1 is drawn to a biopolymer marker(SEQ ID NO:1) which is disclosed as predictive of and/or linked to Alzheimer's disease in the specification as originally filed (see page 46, lines 2-5, Figures 1-2, original claims 1 and 2). Figure 1 evidences the presence of the CENP-E protein (including the claimed peptide, SEQ ID NO:1) in samples obtained from patients age matched with the Alzheimer's disease patients and the absence of the CENP-E protein in samples obtained from Alzheimer's disease patients. Based upon its differential expression the claimed biopolymer marker (SEQ ID NO:1) clearly represents a diagnostic tool for Alzheimer's disease. Thus, Applicants respectfully submit that no further information and/or experimentation is required to prove that the claimed

biopolymer marker is useful. The showing of "differential expression" of the claimed biopolymer marker is sufficient to establish the credibility of the stated utility for the claimed biopolymer marker(SEQ ID NO:1). Thus, Applicants also explicitly show that the claimed biopolymer marker is useful.

Accordingly, Applicants satisfy the requirements of 35 USC 101, by showing that the claimed invention is "useful" for some purpose, for diagnosis and/or therapeutics of Alzheimer's disease, both explicitly and implicitly.

The Examiner states that the claimed peptide (SEQ ID NO:1) is a portion of a mitosis associated peptide, however, no further use or function of the peptide fragment is provided.

An applicant need only make one credible assertion of specific utility for the claimed invention to satisfy 35 USC 101 and 35 USC 112 (see MPEP 2107. 02 I).

Applicants' show the differential expression of the claimed peptide (SEQ ID NO:1) between Alzheimer's disease patients and patients age matched with the Alzheimer's disease patients, which is enough information to establish its usefulness as a marker for Alzheimer's disease. Thus, Applicants have provided one assertion of specific utility and are not required to provide any further use or function of the claimed biopolymer marker (SEQ ID NO:1) to satisfy 35 USC 101 and 35 USC 112.

While the art does not recognize a specific association between the CENP-E protein and Alzheimer's disease, the art does recognize an association between microtubular proteins and Alzheimer's disease.

As a known microtubule motor protein the CENP-E protein is involved with spindle attachment and the mitotic checkpoint (see attached abstract of Yao et al. Nat Cell Biology 2(8):484-491 2000; reference 7).

Axonal terminals are dependent on axoplasmic flow, and that function requires intact microtubules and motor proteins. A significant factor in Alzheimer's disease pathogenesis is the loss of neuronal synapses which occurs due to dis-functional microtubules (see attached abstract of RD Terry Journal of Neural Transmission 53:141-145 1998; reference 8).

Considering that microtubule damage is a known cause of synaptic loss in Alzheimer's disease and the CENP-E protein is necessary for the proper functioning of microtubules, one of skill in the art would find it reasonable to believe that the claimed peptide (SEQ ID NO:1), a fragment of the CENP-E protein, is linked to Alzheimer's disease since the peptide was found to be absent in Alzheimer's disease patients and present in age matched patients. This concept is especially believable in light of the known decrease in the number of microtubules in Alzheimer's disease (see

attached abstract of RD Terry Journal of Neural Transmission 53:141-145 1998; reference 8).

The Examiner asserts that the art acknowledges only certain criteria for definitive diagnosis of Alzheimer's disease and cites three articles which allegedly support her position; Gauthier et al. Canadian Medical Association Journal 157(8):1047-1052 1997; Greicius et al. Journal of Neurology, Neurosurgergy and Psychiatry 72(6):691-700 2002 and Gasparini et al. FASEB Journal 12:17-34 1998. The Examiner asserts that postmortem analysis of brain tissue for the characteristics of amyloid plaques is considered necessary.

The Examiner is reminded that the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it (MPEP 2164.02).

Furthermore, the purpose of the patent system is to promote the progress of science and the useful arts (see "Introduction" of the MPEP and Article 1, section 8 of the US Constitution). Applicants respectfully submit that dismissal of an invention as "useless" simply because it has never been done before does not promote the progress of science and may discourage further medical research. The progress of science usually occurs in a "piecemeal" fashion; meaning that a "discovery" does not arise by itself but often proceeds through multiple "discoveries". For example, a

peptide marker may be considered a small discovery, however, this small discovery contributes to the elucidation of a big discovery, such as a new drug. These smaller discoveries , such as the marker of the instant invention, should therefore be allowed patent protection because they promote the progress of science by leading to further, larger discoveries, i.e. novel diagnostics and/or therapeutics.

The decision in *In re Brana* (34 USPQ2d 1436 and MPEP 2107.01 III) lends support to this argument as well since the Federal Circuit stated:

"Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer".

The prior arts' view of Alzheimer's disease diagnostics does not appear to be as limiting as the Examiner's view. The conventional standard of "definitive diagnosis" by examination of

postmortem brain tissue does not limit the usefulness of other methods suggested for diagnosis. Diagnostic methods other than postmortem examination and brain biopsy have been deemed valuable for diagnosing Alzheimer's disease. For example, Applicants submit their own patent, US 6,451,547 B1 (Jackowski et al.; reference 9) which claims methods for diagnosing Alzheimer's disease by detecting the presence of biochemical markers in bodily fluid.

Even the art cited by the Examiner, deemed to teach the necessity of postmortem examination for diagnosis, explicitly states, "Clinical diagnosis is possible through careful history taking with a reliable informant and a minimum number of laboratory tests". (see the abstract of Gauthier et al. Canadian Medical Association Journal 157(8):1047-1052 1997).

Accordingly, Applicants respectfully disagree with the Examiner's assessment of the state of the art in Alzheimer's disease research and submit that the art teaches that methods other than postmortem examination of brain tissue can be used to reliably diagnose Alzheimer's disease.

Furthermore, it has been settled that an applicant is not required to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt". Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted

utility is more likely than not true (MPEP 2164.07 I C).

Figure 1 establishes that the claimed biopolymer marker (SEQ ID NO:1) is differentially expressed between Alzheimer's disease patients and patients age matched with the Alzheimer's disease patients. As pointed out above, one of skill in the art would recognize differentially expressed peptides to be potential markers for a disease condition. Thus, differential expression of a peptide between a disease state and a normal state is enough information to label a peptide a "marker" for the disease condition, no additional validation or further research is necessary.

Accordingly, Applicants respectfully contend that one of skill in the art would believe, based upon the information in the specification and in light of the knowledge in the prior art, that the claimed biopolymer marker (SEQ ID NO:1) is more likely than not to be a marker for Alzheimer's disease.

It is well settled that if an invention is determined to have "real-world" value, one skilled in the art can use the claimed discovery in a manner that provides some immediate benefit to the public (as established in *Nelson v. Bowler and Crossley* 206 USPQ 881).

The instant invention provides a peptide which was determined to be linked to Alzheimer's disease, thus, unknown samples can be screened for the presence of the peptide in order to link the

sample to Alzheimer's disease. Since new information about the peptide is provided (a link to Alzheimer's disease), no additional research is required in order to use the peptide as a diagnostic tool for identification of the claimed biopolymer marker (SEQ ID NO:1) in a sample and thus, to link the sample to Alzheimer's disease.

The risk for developing Alzheimer's disease increases with age. People are living longer and thus, advances in the diagnosis and treatment of Alzheimer's disease are highly desirable and would greatly benefit the elderly population by delaying symptoms and improving the quality of life for these people. The instant invention discloses a peptide (SEQ ID NO:1) which has already been identified as linked to Alzheimer's disease and thus, represents an advance in Alzheimer's disease research in its current form; a "real-world" use benefitting the public, which satisfies the precedent set in *Nelson*. Thus, the instant invention has "real-world" value.

Furthermore, when considering practical utility ("real-world" utility) relevant evidence is judged as a whole for its persuasiveness in linking observed properties to suggested uses (*Nelson v. Bowler and Crossley* 206 USPQ 881).

The instant specification suggests that the claimed biopolymer marker (SEQ ID NO:1) is useful for diagnostics and/or therapeutics

of Alzheimer's disease since it was found to be differentially expressed in Alzheimer's disease versus an age matched state. Applicants respectfully assert that the observed differential expression is enough evidence such that one of ordinary skill in the art would be reasonably certain of the practical utility of the claimed biopolymer marker (SEQ ID NO:1).

As mentioned above, it has been established that usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. See MPEP 2107. 01 III and *In re Brana* 34 USPQ2d 1436.

The purpose of the patent system is to promote the useful arts. The utility of pharmaceutical inventions in early development has been frequently addressed by the courts.

The situation in the instant case is analogous to that of *Cross v. Iizuka* (MPEP 2107.01 III and 224 USPQ 739). In *Cross*, the Federal Circuit affirmed a finding by the Board of Patent Appeals and Interferences that a pharmacological utility had been disclosed in the application of one party to an interference proceeding. Cross had challenged the evidence in Iizuka's specification that supported the claimed utility. In *Cross*, the Federal Circuit commented on the significance of data from *in vitro* testing that showed pharmacological activity:

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.

The disclosed link between the claimed peptide (SEQ ID NO:1) and Alzheimer's disease will concentrate resources and effort into this peptide, thereby providing immediate benefit to the public, especially the elderly population at risk for the development of Alzheimer's disease. Thus, the claimed peptide (SEQ ID NO:1) should be considered to have practical utility according to legal precedent.

The Federal Circuit again addressed the utility requirement in *Scott v. Finney* (MPEP 2107.01 III and 32 USPQ2d 1115) and *In re Brana* (MPEP 2107.01 III and 34 USPQ2d 1436). The court found that therapeutic utility under the patent laws is not to be confused with the requirements of the FDA with regard to the safety and

efficacy of drugs to be marketed in the United States.

The identification of a protein/peptide showing differential expression in Alzheimer's disease relative to an age-matched control population puts a researcher one step closer to understanding the pathogenesis of Alzheimer's disease and thus, also one step closer to improved diagnosis and treatment of Alzheimer's disease. There is no question that improved diagnosis and treatment of Alzheimer's disease provides a tangible benefit to society; especially for the elderly population susceptible to the development of Alzheimer's disease. Thus, the claimed peptide (SEQ ID NO:1) has a "real-world" use as is, in its currently available form.

Additionally, it is important to point out that Applicants filed many other applications drawn to biopolymer markers for various conditions which are similar to the instant application. Many of these applications were deemed to teach useful, enabled inventions and thus, were issued as patents; US 6,890,722 is particularly relevant, see attached front and claim pages; reference 10).

In conclusion, based upon all of the above arguments, Applicants respectfully submit that one of ordinary skill in the art would immediately appreciate why Applicants regard the claimed biopolymer marker (SEQ ID NO:1) as useful.

Accordingly, Applicants assert that the claimed invention has both a specific and substantial asserted utility and a well established utility, and thus, respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claims 1 and 44 in part, as presented on July 28, 2005, stand rejected under 35 USC 112, first paragraph. Specifically, the Examiner asserts that since the claimed invention is not supported by either a specific and substantial asserted utility and a well established utility, one skilled in the art would clearly not know how to use the claimed invention.

Applicants respectfully disagree with the Examiner's assertions.

It has been established by prior arguments in the instant response that the claimed invention has both specific and substantial asserted utility and a well established utility. Applicants assert that one of skill in the art would know how to use the claimed biopolymer marker (SEQ ID NO:1) as a marker for Alzheimer's disease; therefore, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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